REMARKS

Applicants acknowledge receipt of an Office Action dated December 13, 2004. In this response Applicants have amended claims 25 to correct a typographical error. In addition, Applicants have cancelled claims 33 and 34 without prejudice or disclaimer and have added claims 40-51. Claims 40-49 have been drafted to include subject matter from claims 33 or 34. Claims 50 and 51 find support in the specification, *inter alia*, in the paragraph bridging pages 14-16. Following entry of these amendments, claims 21-32 and 35-51 are pending in the application.

Reconsideration of the present application is respectfully requested in view of the foregoing amendments and the remarks which follow.

Formal Drawings

During a review of their file, Applicants have noted that the PTO has not yet acknowledged acceptance of the formal drawings submitted on August 7, 2003. Applicants respectfully request that the PTO acknowledge acceptance of the drawings in its next communication.

Rejections Under 35 U.S.C. § 102

On page 2 of the Office Action, the PTO has rejected claims 21-32 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent 5,200,198 Geisslinger et al. (hereinafter "Geisslinger").

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See generally MPEP §2131. Here, Geisslinger fails to disclose "administering a composition...to a human subject suffering from a disease influenced by the inhibition of NF-κB production" as recited in independent claim 21. Accordingly, Geisslinger cannot properly anticipate claim 21 and claims 22-32 which ultimately depend therefrom.

With respect to the *Swinehart* case cited at the end of the Office Action. Applicants note that *Swinehart* is not applicable to the facts of this case because the present claims do not

differ merely in terms of stating the causation of the illness, but also in terms of actual differences in the method steps, i.e., the claimed method of treatment, including different dosage ranges.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection under §102.

Rejections Under 35 U.S.C. § 103

On page 3 of the Office Action, the PTO has rejected claims 21-34 and 36-38 under 35 U.S.C. § 103(a) as being unpatentable over Geisslinger and U.S. Patent 5,206,092 to Brune et al. (hereinafter "Brune") in view of Berkow et al. (hereinafter "Berkow"). In addition, on page 5 of the Office Action, the PTO has rejected claims 35 and 39 under 35 U.S.C. § 103(a) as being unpatentable over Geisslinger and Brune in view of Berkow, in further view of U.S. Patent 5,981,592 to Wechter et al. (hereinafter "Wechter") and U.S. Patent 5,840,277 to Ghio et al. (hereinafter "Ghio"). Applicants respectfully traverse these rejections for the reasons set forth below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Here, Geisslinger fails to disclose "administering a composition...to a human subject suffering from a disease influenced by the inhibition of NF-κB production" as recited in independent claim 21 and none of the other cited references, taken either individually or in combination, resolves this deficiency.

Furthermore, Applicants submit that the PTO has failed to establish a proper motivation for combining Geisslinger with Brune and Berkow and that the PTO has also failed to establish a proper motivation for combining Geisslinger with Brune, Berkow, Wechter and Ghio.

In the Office Action, the PTO has relied upon Wechter and Ghio because "Geisslinger et al., Brune et al. and Berkow taken together do not teach expressly to use dosage more than 1000 gm, or to identifying human subject suffering from a disease influenced by the inhibition of NF-kappaB production." See page 5, 2nd full paragraph. The PTO has relied upon Berkow because "Geisslinger et al does not particularly teach the diseases herein, or the dosage herein."

Applicants note that Ghio(newly cited in the present office action) describes the role of NF-kB for inflammation but does not name R-arylpropionic acids as inhibitors of NF-kB. The substances named are alkylaryl polyether alcohol polymers. Further Ghio explicitly states that a chemical structure or property allowing a prediction whether a substance does inhibit NF-kB is not known, see col. 3, lines 59 to 63. The same applies to the old citation of Berkow, which also merely comprises the knowledge of the importance of NF-kB for inflammation and the pain connected with inflammation. Applicants can only conclude that the PTO has used Applicants disclosure as a blueprint for assembling otherwise disparate documents to formulate a rejection.

With respect to Wechter, Applicants note that Wechter relates to the use of R-NSAIDs for the treatment of neoplasias and cystic fibrosis. Both diseases are characterized by an uncontrolled proliferation and only this is treated according to Wechter. The mechanism is given in col. 3, lines 54 to 57 as inhibitor of "influx of neutrophils to the alveolar crevices", a totally different action from NF-kB inhibition. A person of ordinary skill in the art would not find anything in Wechter indicating an action of R-NSAIDs as NF-kB inhibitor.

Applicants respectfully suggest that the very statement of the rejection makes it clear that the PTO has not established a *prima facie* case of obviousness of the claimed invention. Thus, it must first of all be recognized that the discovery and development of physiological treatment agents is a very complex and unpredictable science. Often, it proceeds by a lack of full understanding of the connection between cause and effect of a given illness or condition. Further, even if the cause is identified, the link between treatment agents and the cause is not generally readily apparent. Second, in the present rejection, the PTO admits that the primary references (and/or combination of primary references) do not teach the claimed treatment agents as being effective against conditions that are influenced by inhibition of NF-kB

production. Further, the Office Action admits that the primary references also fail to disclose the dosage range claimed according to the present invention.

Thus, the stated rejection is devoid of any fundamental teaching reference that discloses a single key aspect of the claimed invention! It is simply not possible to rectify such a fundamental lack of teaching in the prior art by combining one or more secondary references, unless that is a very strong motivation in the secondary references to make that combination, i.e., unless there is a clear suggestion of a likelihood of success of accomplishing the claimed method of treatment. Here, the secondary references are likewise devoid of any clear teaching of the invention and/or motivation for combining them in such a way that one would arrive at the claimed invention.

It is textbook patent law that a claim of treating condition X with agent Y in a dosage Z can be patentable based on the novelty of any one (or more) of X, Y or Z. Further, such a claim is not anticipated by the mere fact that some patients, who may have had condition X as a co-condition (known or unknown) to another condition under treatment, *may* have been unknowingly and/or incidentally treated with agent Y, even in dosage Z, while being treated for the other condition. Once novelty is established for the claimed treatment method, the very high level of unpredictability in the pharmaceutical field makes it extremely difficult for the PTO to establish a *prima facie* case of obviousness for the method, absent a clear recognition of a cause and effect relationship between X and Y, and particularly at dosage Z. Such a recognition is simply absent in the prior art applied to the present claims.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections under §103.

Newly Added Claims

In this response, Applicants have added claims 40-49. With respect to claims 40-49, Applicants note that the diseases referenced in claims 33 and 34 and influenced by NF-κB can be separated into the following groups:

1. rheumatic diseases;
2. tumors, immune diseases;
3. asthma, shock, inflammatory intestinal diseases; and

4. radiation damage, arteriosclerosis, rejection reaction after organ and tissue transplantation.

The first group of indications are rheumatic diseases. The use of arylpropionic acids for those diseases had been ascribed to COX-inhibition and some other mechanisms, which implied a treatment of the pain and a suppression of inflammation without any positive influence on the inflammation as such, see Martindale, Pharmacopoeia, page 12, left column second sentence. The corticosteroids, also used for treatment of rheumatic diseases and known to be NF-κB-inhibitors, not only suppress the inflammation, they are believed to actually influence the process. In Martindale, page 12, column in the middle, third paragraph at the end, it is stated that the bone loss associated with rheumatoid diseases is reduced. NF-κB-inhibitors like the corticosteroids are not administered to relieve acute pain but to treat the inflammation. Therefore, the treatment according to the present invention will involve administering the substances over prolonged periods independently of pain. This would clearly be a wrong therapy when medicaments are used that only relieve the symptoms and do not influence the disease behind them.

The second group encompasses diseases that are influenced positively by arylpropionic acids via mechanisms totally unassociated with the effect on pain.

The third group comprises diseases that have so far been thought to be a contraindication to the use of arylpropionic acids in the known treatment of pain, or are known side effects of this treatment. It cannot be known or obvious to use a substance that is contraindicated.

Finally, the last group are diseases that have heretofore never been mentioned in connection with arylpropionic acids. The use of arylpropionic acids for treatment of pain, cannot teach the present invention any more than can the use of paracetamol for relief of pain associated with sinusitis would teach an antibacterial activity of paracetamol (which is of course not present). The situation with such an hypothetical antibacterial effect of paracetamol would be analogous, the use for the "indication" as such is known, the actual use would differ nonetheless. Medicaments for pain relief should only be taken if and as long as there is pain. A substance with antibacterial effect should be used as long as there are bacteria to be killed, regardless of pain being felt or not. This example shows that it is not proper to simply rely on a name of a disease to define whether a second medical use is

claimed or not. The finding of a new and unknown way of action (at a different dosage level and/or over a different treatment regimen) can be as much a second medical use as the finding of an effect on a different disease.

With respect to claim 50 and 51, Applicants note that none of the cited references, taken either individually or in combination, teach or suggest administering the composition "for a period sufficient to treat the disease influenced by the inhibition of NF-κB production" or the step of "identifying a human subject suffering from a disease influenced by the inhibition of NF-κB production."

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

Respectfully submitted,

Date 6/13/05

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5540
Facsimile: (202) 672-5399

Richard L. Schwaab
Attorney for Applicants
Registration No. 25,479

Paul D. Strain
Agent for Applicants
Registration No. 47,369

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.